IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Andrew VAILLANT et al.
Serial number:	10/661,097
Filing date:	September 12, 2003
For:	ANTIVIRAL OLIGONUCLEOTIDES TARGETING HSV AND CMV
Art Unit:	1635
Examiner:	Jane J., ZARA
Agent:	Christian Cawthorn (514) 847-4256

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
U. S. A.

Sir:

Please find enclosed herewith form PTO/SB/33 for the pre-appeal brief request for review. Please consider the reasons below for which the review is being requested.

A Notice of Appeal is being filed concurrently.

REASONS:

Sequence compliance

As requested by the Examiner, the specification and the drawings have been amended to provide SEQ ID NOs for the oligonucleotide sequences disclosed throughout the specification.

Election/Restrictions

Claims 3-13, and 33-38 have been cancelled, as requested by the Examiner.

Claim rejections - 35 U.S.C. § 112

Rejections 1, 2 and 14-32 have been rejected under 35 U.S.C. 112, first paragraph, for containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention, was maintained by the Examiner. In this regard, the Applicants wish to submit that claim 1 has been amended to further define that the oligonucleotides claimed comprise at

Assistant Commissioner for Patents

least one phosphorothioated linkage and are at least 30 nucleotides in length. Consequently, the distinguishing features or common attributes concisely shared by the members of the genus claimed in the present application is that the oligonucleotides have at least one phosphorothioated linkage, at least 30 nucleotides in length and an antiviral activity occurring by a non-sequence complementary mode of action. The oligonucleotides claimed do not have any other common feature other than being at least 30 nucleotides in length (as exemplified in the application with REP 2005, REP 2006, REP 2007, REP 2008, SEQ ID NO: 6, SEQ ID NO: 9, REP 2024, SEQ ID NO: 20, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 26, REP 2060, SEQ ID NO: 22 and SEQ ID NO: 24) and having at least one phosphorothioated linkage. Furthermore, the oligonucleotides used in the present invention and claimed in claims 1, 2 and 14, 15, 17, 18, 21, 22 and 27-29 can be randomer oligonucleotides. As defined on page 14 of the present description, the term "randomer" is intended to mean a single stranded DNA having a wobble (N) at every position, such as NNNNNNNNNN. Each base is synthesized as a wobble such that the randomer oligonucleotides of the present invention actually consist of a population of different randomly generated sequences of the same size. By the nature of the preparation used to produce them, sequence complementary mode of action cannot occur. For example, in a 15 μmol preparation of a randomer oligonucleotide containing 31 nucleotides in length, this preparation will have at most 2 copies of every possible sequence of nucleotides. Thus, the presence of 2 copies of a specific sequence cannot account for the response observed in the present invention. Consequently, the antiviral activity of the oligonucleotides claimed in the present application and demonstrated for at least 14 different oligonucleotides *in vitro* (see Example 1, 2, 3 and Figs. 1-5, 7, 8, 11-18 and 37) and for 3 oligonucleotides *in vivo* (see Declaration filed October 5, 2006), is not due to a sequence specificity and complementary mode of action. Thus, Applicants are entitled to claim an oligonucleotide (without reference to a specific sequence) having at least one phosphorothioated linkage and an antiviral activity occurring principally by a non-sequence complementary mode of action.

Further, the Applicants wish to point out that the Manual of Patent Examining Procedure mentions that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a

> claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the genus" (Manual of Patent Examining Procedure 2163.05).

The Applicants' results, as acknowledged by the Examiner, are disclosed in the present application demonstrating the antiviral activity of the oligonucleotides claimed in the present application against HSV-1, HSV-2 and CMV. More specifically, results demonstrating the antiviral activity of at least 14 different oligonucleotides of at least 30 nucleotides in length (for example REP 2005, 2006, 2007, 2018, 2018, 2021, 2024, 2029, 2030, 2031, 2055, 2056, 2057 and 2060) against HSV-1, HSV-2 or CMV *in vitro* are disclosed in Example 1, 2, 3 and Figs. 1-5, 7, 8, 11-18 and 37. Furthermore, as submitted in a Declaration filed October 5, 2006, results demonstrating the *in vivo* efficacy of two oligonucleotides (REP 2006 and 2031) to prevent HSV-2 transmission in a mouse model, as well as three oligonucleotides (REP 2006, 2031 and 2107), to reduce CMV liver titers upon intraperitoneal administration have been disclosed. Thus, the antiviral activity of the oligonucleotides claimed in the present application has been demonstrated for 14 different oligonucleotides which is believed to be a "representative number of species". Consequently, it is believed that the present application teaches a sufficient and/or representative number of varieties of species to reflect the complete genus. It is thus believed that the Examiner's rejection of claims 1, 2 and 14-32 under 35 U.S.C. § 112, first paragraph, is improper, and requests that it be withdrawn.

Rejection of claims 1, 2, and 14-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, was maintained. In this regard, the Applicants respectfully submit that it is clearly stated in the Manual of Patent Examining Procedure that:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility.
>
> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. (Manual of Patent Examining Procedure 2107.03).

It is thus believed that not only the Applicants have provided *in vitro* results demonstrating the antiviral activity of at least 14 different oligonucleotides of at least 30 nucleotides in length, but the results were correlated by the *in vivo* results demonstrating the efficacy of two oligonucleotides (REP 2006 and 2031) to prevent HSV-2 transmission in a mouse model, as well as three oligonucleotides

Assistant Commissioner for Patents

(REP 2006, 2031 and 2107), to reduce CMV liver titers upon intraperitoneal administration have been disclosed. Also, the Examiner **agrees** that *in vivo* efficacy has been shown for the particularly described oligonucleotides, REP 2006, 2031 and 2107, regarding the ability to prevent or reduce HSV-2 or CMV infection in an appropriate animal model. Consequently, Applicants believe that a reasonable correlation between the activity in question and the asserted utility has been demonstrated in the present application. The Applicants respectfully disagree with the Examiner's argument that the ability of the oligonucleotides tested *in vivo* to treat or prevent HSV-2 and CMV is not correlative or representative of the ability to predict the efficacy of any randomers of 30 bases, as now claimed, or more to provide such effects in a subject. A person skilled in the art would acknowledge that extensive data, reflecting a sufficient and/or representative number of varieties of species to reflect the complete genus, was disclosed in order to demonstrate the antiviral activity of the oligonucleotide of the present invention *in vitro*. Further, three oligonucleotides, two of which are randomers and thus assume any sequence as presented hereinabove, have been used to demonstrate the ability to predict the efficacy of any randomers of 30 bases or more in animal models. The Applicants also respectfully submit that the HSV-2 mouse model and the CMV mouse model used to demonstrate the ability of the oligonucleotides tested *in vivo* to treat or prevent HSV-2 and CMV are well accepted *in vivo* models for the study of pathogenesis and antiviral compound activity (Krmpotic *et al.*, 2003, Microbes and Infection, 5: 1263-1277; Scott *et al.*, J General Virology, 86: 2141-2151; Bernstein *et al.*, 2003, Antimicrobial Agents and Chemotherapy, 47: 3784-3788; Bourne *et al.*, 1999, J Infectious Diseases, 180: 203-205).

In addition, the Applicants believe that in order to convince the Examiner of the enablement of the present invention, under her requirement, clinical trials would have been initiated before this application would have been filed. Requesting clinical trial results to demonstrate enablement of the present invention is unreasonable and represents an undue burden, burden that does not exist in any other field of invention. Applicants respectfully submit that it is stated in the Manual of Patent Examining Procedure (MPEP 2107.03, section IV) that "*Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders*".

The Applicants wish to submit that, only when the pre-clinical data is promising, a company makes a decision on whether to begin the long and costly process of clinical trials. Most companies file for and receive patents for the commercial uses of the compound that they are developing during pre-clinical trials to not only protect their invention, but also to reassure investors that the invention

Assistant Commissioner for Patents

which will be undergoing clinical phase trials is patented. Assuming the company decides to pursue human studies, it must first submit an Investigational New Drug (IND) application to the FDA for approval. The IND must provide pre-clinical data of sufficient quality to justify the testing of the drug in humans. It is believed that in order for the present invention to be commercially and financially liable, Applicants need to file a patent application before submitting an IND application to the FDA. The Applicants believe that the Examiner is not examining the present application in terms of its patentability, but in terms of its liability to pursue human studies, which is believed to be the role of the FDA and not of the USPTO. Consequently, Applicants feel that, in view of the arguments presented by the Examiner, it is easier to obtain an FDA approval to start clinical phase trials than meeting the criteria of patentability imposed by the Examiner. Further, it is believed that the Examiner is requesting further testing in animal models of a larger number of oligonucleotides in order to demonstrate the ability of 30 bases or more oligonucleotides to treat or prevent HSV-1, HSV-2 and CMV infection.

In view of the foregoing, the Applicants believe that the Examiner's rejection of claims 1, 2 and 14-32 under 35 U.S.C. § 112, first paragraph, is improper, and requests that it be withdrawn.

It is submitted, therefore, that the claims are in condition for allowance, and prompt and favorable action in the form of a Notice of Allowance is earnestly solicited.

Respectfully submitted,

Date: May 18, 2007

By: /Christian CAWTHORN/

Christian Cawthorn, Reg. No. 47,352
Agent for Applicants
Tel: (514) 847-4256

OGILVY RENAULT LLP
1981 McGill College, Suite 1600
Montreal, Quebec H3A 2Y3
CANADA